DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 341, and 369

[Docket No. 76N–052H]

RIN 0905–AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of Final Monograph for OTC Antihistamine Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the final monograph for over-the-counter (OTC) antihistamine drug products to include the ingredient doxylamine succinate. FDA is issuing this final rule after considering extensive information concerning this ingredient and the recommendations of its Nonprescription Drugs Advisory Committee (NDAC), which met on June 28, 1993, to consider potential labeling for doxylamine succinate regarding the results of toxicology testing conducted under the National Toxicology Program (NTP). This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: January 30, 1995.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. In that notice, the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel) recommended that doxylamine succinate be generally recognized as safe and effective (Category I) as an OTC antihistamine at a dosage level of 7.5 to 12.5 milligrams (mg) (41 FR 38312 at 38385 through 38387). At that time, the agency concluded that doxylamine succinate should remain a prescription drug at dosage levels above 7.5 mg because it causes a high incidence of drowsiness compared to other OTC antihistamines (41 FR 38312 at 38313). Subsequently, after evaluating extensive data on the safety of doxylamine succinate, the agency determined that doxylamine succinate could be marketed OTC at the Panel's recommended dosage. In the **Federal Register** of August 24, 1987 (52 FR 31892 at 31893 through 31903), the agency proposed monograph status at dosages of 7.5 to 12.5 mg. No comments were received in response to this proposal.

In 1991, the agency received a report of a study on doxylamine succinate conducted by the National Center for Toxicological Research (NCTR) (Ref. 1). The results of this study were under consideration when the agency published the final monograph on OTC antihistamine drug products on December 9, 1992 (57 FR 58356). Accordingly, the agency deferred a decision on doxylamine succinate at that time.

The NCTR technical report concerns a 2-year carcinogenicity and chronic toxicity study of doxylamine succinate in Fischer 344 rats and B6C3F1 mice. The study was conducted under the auspices of the NTP. The study was prompted by the National Cancer Institute's finding that methapyrilene, a similar antihistamine, is a potent liver carcinogen in the rat (Ref. 2). Methapyrilene was removed from the market in 1979. The NCTR study on doxylamine succinate was reviewed by the agency's Pulmonary-Allergy Drugs Advisory Committee (the P-A Committee) on June 13 and 14, 1991 (Ref. 3).

In the NCTR study (Ref. 1), doxylamine succinate was administered, ad libitum, as an admixture in the feed to male and female rats at dose levels of 0, 500, 1,000, or 2,000 parts per million (ppm) for 2 years. Mice of both sexes received food containing dose levels of 0, 190, 375, or 750 ppm. Each group contained 48 weanling animals per sex; the animals were scheduled for sacrifice at the end of 104 weeks. An additional group of animals (9 rats and 12 mice per sex) in each dose group was sacrificed at the end of 65 weeks. There were no significant treatment-related differences in survival in either rats or mice. In rats, the highest doxylamine succinate dose group had final body weights that were 22.8 percent (females) and 8.4 percent (males) lower than controls. A number of nonneoplastic lesions was observed in rats, including fatty change, degeneration, and hyperplasia of the liver and increased cytoplasmic alteration in the salivary glands. In mice, there was evidence of hepatotoxicity including hypertrophy, clear and mixed cell foci, and, in females, fatty change. There also was a treatment-related increase in "atypical" hepatocytes in male mice. Both male and female mice had a dose-related increase in thyroid follicular cell hyperplasia. There was a positive trend for increased incidence with increasing dose for both hepatocellular adenomas and carcinomas in male rats. When the incidence of adenomas and carcinomas was combined, the statistical test was positive ($p < 0.01$) and the incidence in the highest dose group was significantly ($p < 0.05$) increased over that of controls. No treatment-related increase in neoplasms was found in female rats. Although not statistically significant, one rat in each of the high dose groups of male and female rats was found to have a pineal gland tumor, which is an extremely rare neoplasm in rats. In mice, doxylamine succinate administration produced an increased incidence of hepatocellular adenoma in both males ($p < 0.001$) and females ($p < 0.001$). Also, there was an increased incidence of follicular cell adenoma of the thyroid gland in male ($p < 0.05$) and female ($p < 0.0001$) mice.

Although the rodent tumorigenicity studies were positive, doxylamine succinate tested negative overall in in vitro tests for genotoxic activity (causing damage to deoxyribonucleic acid (DNA)). Based on the overall assessment, the tumorigenic responses observed in the rodent bioassays may relate to secondary mechanisms involving the induction of liver microsomal enzymes, cytotoxicity, cell proliferation, promotion of tumor potential in pre-existing susceptible cells, or other processes. Such mechanisms may represent species-specific effects or threshold phenomena applicable to rodents (under the conditions of the bioassay), but these mechanisms are considered of questionable significance in humans.

Due to uncertainty concerning the relevance of these findings to human use, the agency asked its P-A Committee and a number of consulting experts to evaluate the data and to advise the agency on whether doxylamine succinate should continue to be marketed OTC. By a vote of five to one, the P-A Committee concluded at its June 13 and 14, 1991, meeting that doxylamine succinate is not likely to have human carcinogenic potential. Again, by the same vote, the P-A Committee recommended that doxylamine succinate could remain OTC, but that consumers should be alerted that these data exist. The P-A Committee discussed labeling as a preferred means of providing this

information (Ref. 3, pp. 175 through 182).

FDA subsequently developed possible labeling that could be used. This labeling included the warning: "Use of this product may be hazardous to your health. This product contains doxylamine succinate which has been determined to produce tumors in laboratory animals." The agency requested the views of a national trade association of OTC drug manufacturers on this suggested warning (Ref. 4). In response, the association asserted that such a warning would be inappropriate (Ref. 5). The association stated that such a warning: (1) Would not ensure safe and effective product use by consumers; (2) is not based on sound scientific data known to be relevant to the human condition; (3) is not understood and actionable, in a meaningful way, by consumers; and (4) might reduce the impact of other warnings and occupy scarce label space.

The association argued that the proposed warning does not meet the criteria of section 502(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(c)). This part of the statute requires labeling information to be presented in "terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use." The association contended that the proposed warning effectively shifts the burden of determining product safety from the agency to the consumer and then does not tell the consumer what action to take. In a subsequent communication (Ref. 6), the association further argued that a warning statement in the labeling of doxylamine products is not justified because the scientific data do not suggest a significant risk to humans, that such a warning would be unprecedented, and that a label warning is not the appropriate means for disclosing this information.

In 1992, the agency established a new advisory committee specifically for the review of OTC drugs, the Nonprescription Drugs Advisory Committee (NDAC). The agency asked NDAC to consider the issue of a tumor statement in the labeling of OTC drug products containing doxylamine succinate at its June 28, 1993, meeting. The agency presented a summary of the NCTR data, possible labeling, and legal and compliance issues (Ref. 7). Other interested parties presented their positions. The agency asked NDAC to consider the following questions: (1) Should a labeling statement be used to inform consumers in place of other alternative approaches (no warning, prescription only status, removal from all marketing, etc.)? (2) Is there a desirable risk-to-benefit relationship for labeling? (3) If the answer to both questions is yes, what information should be included in the labeling and what language should be used that would be easily understood by the average consumer? (4) How should information be presented to the consumer (i.e., under the "Warning" or some other heading, visible at the point of purchase, on the immediate container, or in a package insert) and should the information indicate that the product could be "hazardous" to health?

After considering the available evidence, NDAC voted unanimously (10 to 0) to reaffirm the P-A Committee's recommendation that doxylamine succinate remain OTC. NDAC also recommended (10 to 0) that there be no specific statement about tumors in the labeling and urged FDA to write a fully descriptive article on the subject in the "FDA Consumer" magazine.

The agency has considered the two advisory committees' recommendations and concludes that doxylamine succinate is safe and effective for OTC use as an antihistamine. Accordingly, the agency is including doxylamine succinate in the final monograph for OTC antihistamine drug products. The agency is also developing an "FDA Consumer" article and has issued a talk paper concerning the NCTR findings in animals to inform consumers of these data and the uncertainty of their relevance to humans.

References

(1) Department of Health and Human Services, NCTR, "Technical Report for Experiments 406 and 407; Chronic Study of Doxylamine in Fischer 344 Rats and B6C3F1 Mice," 1991, in OTC vol. 04HFM, Docket No. 76N–052H, Dockets Management Branch.

(2) Lijinsky, W., M. D. Reuber, and B. N. Blackwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," Science, 209:817–819, 1980.

(3) Transcript of the June 13 and 14, 1991, meeting of the FDA Pulmonary–Allergy Drugs Advisory Committee, coded RPT 5, Docket No. 76N–052H, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to R. W. Soller, NDMA, coded LET 91, Docket No. 76N–052H, Dockets Management Branch.

(5) Letter from R. W. Soller, NDMA, to W. E. Gilbertson, FDA, coded C216, Docket No. 76N–052H, Dockets Management Branch.

(6) Letter from R. W. Soller, NDMA, to W. E. Gilbertson, FDA, coded C224, Docket No. 76N–052H, Dockets Management Branch.

(7) Transcript of the June 28, 1993, meeting of the FDA Nonprescription Drugs Advisory Committee, vol. I, pp. 6–89, coded TR 2, Docket No. 76N–052H, Dockets Management Branch.

The agency has examined the economic consequences of this final rule and has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12866, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354). This rulemaking for OTC antihistamine drug products is not expected to have an impact on small businesses. Doxylamine succinate remains available OTC. No product reformulations will be required. Some minor relabeling will be necessary to meet the conditions of the final monograph. Manufacturers will have 1 year to implement this relabeling. Thus, the impact of the final rule appears to be minimal. Therefore, the agency concludes that the final rule is not a major rule as defined in Executive Order 12866. Further, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

The agency is removing the exemption for certain drugs limited by new drug applications (NDA) to prescription sale in § 310.201(a)(13) (applicable to doxylamine succinate preparations) because most portions of that exemption are superseded by the requirements of the antihistamine final monograph (21 CFR part 341). Section 310.201(a)(13) does not apply to the use of doxylamine succinate as a nighttime sleep-aid, for which an NDA is required for marketing.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 341

Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310, 341, and 369 are amended as follows:

PART 310—NEW DRUGS

2. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

§ 310.201 [Amended]

2. Section 310.201 *Exemption for certain drugs limited by new-drug applications to prescription sale* is amended by removing paragraph (a)(13) and reserving it.

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).4. Section 341.12 is amended by adding new paragraph (h) to read as follows:

§ 341.12 Antihistamine active ingredients.

* * * * *

(h) Doxylamine succinate.

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5. Section 341.72 is amended by revising the heading of paragraphs (c)(4) and (c)(6)(iii) and by adding new paragraph (d)(8) to read as follows:

§ 341.72 Labeling of antihistamine drug products.

* * * * *

(c) * * *

(4) *For products containing diphenhydramine citrate, diphenhydramine hydrochloride, or doxylamine succinate identified in § 341.12(f), (g), and (h).* * * *

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(6) * * *

(iii) *For products containing diphenhydramine citrate, diphenhydramine hydrochloride, or doxylamine succinate identified in § 341.12(f), (g), and (h).* * * *

(d) * * *

(8) *For products containing doxylamine succinate identified in § 341.12(h).* Adults and children 12 years of age and over: oral dosage is 7.5 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 3.75 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

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6. Section 341.90 is amended by adding new paragraph (l) to read as follows:

§ 341.90 Professional labeling.

* * * * *

(l) *For products containing doxylamine succinate identified in § 341.12(h).* Children 2 to under 6 years of age: oral dosage is 1.9 to 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours.

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PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

7. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.21 [Amended]

8. Section 369.21 Drugs; warning and caution statements required by regulations is amended by revising the introductory text of the entry for "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, DOXYLAMINE SUCCINATE, AND CHLOROTHEN CITRATE PREPARATIONS)" to read "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE AND CHLOROTHEN CITRATE PREPARATIONS). (See § 310.201(a)(4) and (a)(24) of this chapter.)"

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Dated: January 24, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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